



Communication

STK11 Mutated Lung Adenocarcinoma: A Molecular and Clinicopathologic Study

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Abstract

Targetable gene alterations have become increasingly important in the treatment of cancers. Thirty *STK11*-mutated lung cancers from 199 cases with molecular profiling performed during 2016–2024 were studied for clinical, morphologic, immunohistochemical (IHC) and molecular features. Of the 30 *STK11*-mutated lung cancers, 29 were lung adenocarcinomas (LADCs) and 1 was large cell neuroendocrine carcinoma (LCNEC). *STK11* mutation was not found in other subtypes of lung cancers. Of the 29 *STK11*-mutated LADCs, 6 (21%) were mucinous and 23 (79%) were non-mucinous. Of the 19 non-mucinous LADCs with sufficient material for IHC, 9 (47%) displayed acinar/papillary/lepidic patterns, 8 (42%) were poorly differentiated (solid/trabecular/basaloid/complex glandular), and 2 (11%) had mixed solid and acinar patterns. The most common concurrent altered genes were *KRAS* (52%), followed by *TP53* (38%), *KEAP1* (34%), and DNA repair genes (*BRCA2/ATM*) (21%). A total of 6/15 (40%) LADCs with a *KRAS* mutation presented with mucinous morphology. Concurrent *EGFR*, *ROS*, or *ALK* alterations with *STK11* mutation were rare or non-existent. Of the 3 LADCs with *SMARCA4* deficiency, 2 were mucinous and 1 had basaloid/adenoid cystic-like features. All the cases were microsatellite stable (MSS). The majority (55%) had low TMB (<10). Most (86%) had PD-L1 TPS 0 or <5%. Among the 14 non-mucinous LADCs with IHC performed, 5 (36%) were TTF-1-negative and all displayed poorly differentiated morphology. Overall, 8/10 (80%) of poorly differentiated components in non-mucinous LADCs were negative for TTF-1. In contrast, all LADCs with better differentiated patterns (acini/papillary/lepidic) were positive for TTF-1. The majority (14/21, 67%) of patients with available follow-up presented with metastasis.

Keywords: STK11; lung cancer; molecular; TTF-1; growth pattern



Academic Editor: Izidor Kern

Received: 23 September 2025

Revised: 5 November 2025

Accepted: 12 November 2025

Published: 17 November 2025

Citation: Jean, J.; Wallace, W.D.; Xiao, G.-Q. *STK11* Mutated Lung Adenocarcinoma: A Molecular and Clinicopathologic Study. *J. Mol. Pathol.* **2025**, *6*, 28. <https://doi.org/10.3390/jmp6040028>

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1. Introduction

Adenocarcinoma is the most common malignancy in the lung. Lung adenocarcinoma (LADC) can be further subclassified into mucinous and non-mucinous subtypes. Smoking is the most common risk factor for lung cancers [1], including LADC. With the advancement of molecular techniques and cancer research, targetable gene alterations have become increasingly important in the treatment of cancers. For example, EGFR-targeted therapy has become a cornerstone in the management of advanced LADCs [2,3].

Serine/threonine kinase 11 (*STK11*), encoding liver kinase B1 (LKB1), is a tumor suppressor gene [4,5]. Germline loss-of-function mutation in *STK11* gives rise to Peutz-Jeghers syndrome [5,6], which is associated with a substantially increased lifetime risk of

many cancers [5,7]. In the sporadic setting, *STK11* mutations have also been found in a subset of LADCs [5,8–10]. Although *STK11*-mutated lung cancers have been sporadically studied, many aspects, including histopathologic features, remain to be elucidated.

In clinical pathology practice, differentiation of primary lung carcinoma versus metastatic adenocarcinoma mainly relies on immunohistochemical (IHC) marker study, in particular, TTF-1 and Napsin A expression in LADC [11]. TTF-1 is reported to be positive in ~90% non-mucinous LADC [12,13]. Whereas, for mucinous LADC, TTF-1 is often negative [14]. The TTF-1/Napsin A-negative non-mucinous LADCs have, so far, not been well characterized.

The aim of this study is to investigate the histomorphologic, IHC, clinical, and molecular features of *STK11*-mutated LADCs.

2. Materials and Methods

Clinical Cases and Tissue Samples

This study was approved by the USC Institutional Review Board (HS-24-00234). A total of 199 cases of primary and metastatic lung cancers from needle biopsy or resection specimens accessioned at our institution from 2016 to 2024 with comprehensive molecular profiling were found. *STK11* mutation was identified in 30 cases (29 LADCs and 1 large cell neuroendocrine carcinoma (LCNEC)). The lung origin and adenocarcinoma subtype were confirmed by clinical and imaging studies, IHC (TTF-1/Napsin A), and/or mucicarmine stain. Other IHC markers (e.g., p40, CK7) commonly used in the workup for lung cancer and markers for exclusion of metastasis of non-lung origin were also performed when appropriate. Neuroendocrine carcinoma was confirmed by neuroendocrine markers (synaptophysin/chromogranin/CD56/INSM1).

Clinical and Pathologic Assessment

Given that the vast majority of *STK11*-mutated lung cancers were LADCs, this study mainly focused on *STK11*-mutated LADCs. All the 29 *STK11*-mutated LADCs were reviewed for their molecular features, IHC profile, and, when tissue was available for review, blindly by two pathologists for their morphologic growth patterns (defined by WHO). Patients' demographic information, smoking history, and clinical follow-up data (from 7 months to 8 years) were also recorded.

Immunohistochemistry

IHC stains were performed on some of the cases based on clinical needs at the time of original case sign-out. The IHC stains were performed with a Bond III automated immunostaining platform (Leica Biosystems, Nussloch, Germany) using standard clinical protocols with appropriate positive and negative controls. Briefly, unstained glass slides of 5 µm thick tissue sections were baked and dewaxed following standard procedures. Heat-induced epitope retrieval was performed using BOND Epitope Retrieval Solution 1 (ER1) or BOND Epitope Retrieval Solution 2 (ER2) (Leica Biosystems) at 100 °C for 30 min. The antibodies used included TTF-1 (SPT24, Leica, Wetzlar, Germany), Napsin-A (TMU-Ad02, Biocare, Pacheco, USA), p40 (BC28, Biocare), CK7 (RN7, Leica), and neuroendocrine markers (Synaptophysin (27G12, Leica), Chromogranin (5H7, Leica), CD56 (CD564, Leica), and INSM1 (A-8, Santa Cruz, USA), among others. The IHC stains were recorded as positive (at least 10% of tumor cells with moderate or strong stain) or negative for each case, as well as for the poorly differentiated and better differentiated components when both were present in the same tumor.

Gene Sequencing and Molecular Analysis

The genetic alterations, including tumor mutation burden (TMB), microsatellite stability (MSS), and PD-L1 tumor percentage score (TPS), were analyzed by Caris Molecular Intelligence comprehensive tumor profiling services (Caris Life Sciences, Irving, USA) [15]. Briefly, Caris's MI Profile Tumor Seek Hybrid was used along with the IHC in this study.

IlluminaNovaSeq 6000 sequencers (San Diego, USA) were used to perform whole exome sequencing (WES) and whole transcriptome sequencing (WTS), which could detect 23,000+ genes, with more than 700 of these genes being documented as clinically relevant. Sequencing results were analyzed by Caris NGS bioinformatic pipeline, and reports were provided by Report Generation software (v4.4). Microsatellite instability status was detected in this assay. Tumor-only MSI status by NGS was determined by the direct analysis of known microsatellite regions sequenced. Tumor mutational burden (TMB) was determined by the number of non-synonymous, somatic mutations per one megabase (Mb) of sequenced DNA in the tumor sample. The cut-offs for low TMB and high TMB were <10 and ≥ 10 mut/Mb, respectively. IHC antibodies were also used in combination with the MI Tumor Seek Hybrid assay. PD-L1 22c3 (Dako, Santa Clara, USA) IHC was used for tumor proportion score (TPS) calculation. The TPS was grouped into three categories based on membranous staining of viable tumor cells: less than 1%, 1–49%, and at least 50%, which corresponded to negative, low positive, and high positive, respectively. It needed complete or partial membranous staining of viable tumor cells. The results were then compiled into a final report. More specific details of the methods used, including the bioinformatics pipeline, can be potentially obtained by directly contacting Caris.

3. Results

Clinical And Morpho-Pathologic Features of *STK11*-Mutated LADCs

Of the 199 lung cancer cases with molecular profiling performed, 112 were LADCs, 68 squamous cell carcinomas, 7 adenosquamous carcinomas, 4 adenoid cystic carcinomas, 4 large cell neuroendocrine carcinomas (LCNEC), 2 small cell carcinomas, and 2 spindle cell/pleomorphic carcinomas. Of the 199 cases, 30 (15%) had the *STK11* mutation. Of the 30 cases with *STK11* mutation, 29 were LADCs, accounting for 26% of the 112 LADCs studied, and 1 was LCNEC. None of the squamous cell carcinomas, adenosquamous carcinomas, adenoid cystic carcinomas, or pleomorphic carcinomas showed *STK11* mutation. Patients' ages ranged from 59 to 92 years old (mean 74 ± 9) with male predominance (the ratio of male to female was 4:1). Most patients (24/30, 80%) were current or former smokers, and almost all (28/30, 93%) had more than 10 years of smoking history.

Of the 29 *STK11*-mutated LADCs, 6 (21%) were mucinous and 23 (79%) were non-mucinous. Of the 23 non-mucinous LADCs, 19 contained adequate tissue for assessment of growth patterns. Of these 19 cases, 9 (47%) displayed acinar/papillary/lepidic growth patterns, 8 (42%) showed poorly differentiated (solid/nested/trabecular/basaloid/complex glandular/cribriform patterns), and 2 (2/19, 11%) had mixed solid and acinar patterns.

TMB, Other Concurring Gene Alterations, And Histopathologic Correlation for *STK11*-Mutated LADCs

TMB for these *STK11*-mutated LADCs ranged from 2 to 17 (mean 8.6 ± 3.8). A total of 16/29 (55%) had low TMB (<10), and 13 (45%) had moderate to high TMB (≥ 10). A total of 15/29 (52%) LADCs had a *KRAS* mutation, of which 6/15 (40%) presented with mucinous morphology.

Tumor suppressor genes were the second most common concurring alterations: 11/29 (38%) with *TP53* mutation, 1 with *MDM2* amplification, and 1 with *APC* alteration.

KEAP1 alterations were present in 10/29 (34%) LADCs. None of the LADCs with combined *STK11* and *KEAP1* mutations was associated with mucinous morphology, even in the setting of a *KRAS* mutation.

DNA repair gene (*BRCA2*, *ATM*) alterations were not uncommon and seen in 6/29 (21%) cases. DNA repair gene alteration and tumor suppressor gene (*TP53*/*MDM2*/*APC*) alterations appeared to be mutually exclusive. Concurrent *EGFR* and *STK11* alterations

were exceptionally uncommon and seen in only 1/30 (3.3%) cases. No *ROS* or *ALK* alterations were found in this series.

Of note, there were 3 LADCs with *SMARCA4* deficiency, 2 of which were mucinous and 1 basaloid/adenoid cystic-like.

MSI, PD-L1, and IHC Features of *STK11*-Mutated LADCs

All 30 *STK11*-mutated lung cancer cases were microsatellite stable (MSS).

Of the 29 *STK11*-mutated LADCs, 20/29 (69%) had PD-L1 TPS 0; 7/29 (24%) had PD-L1 TPS 1–49%; the remaining 2 LADCs (7%) had high ($\geq 50\%$) PD-L1 TPS (90% and 100%, respectively). Both cases with high PD-L1 TPS had *ATM* and *KEAP1* alterations.

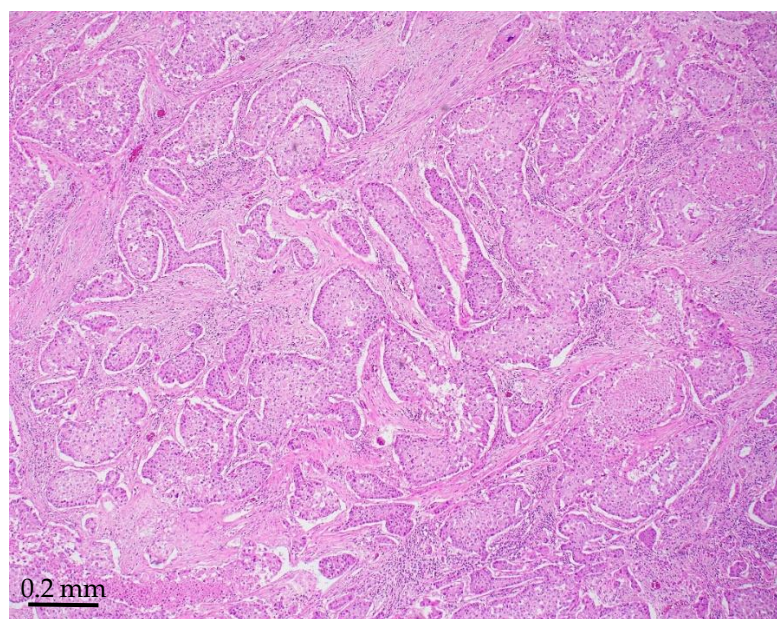
Among the 15 cases with IHC performed, TTF-1/Napsin A negativity was seen in 1 LC-NEC and 6/15 (40%) of LADCs (1 mucinous and 5 non-mucinous). The growth pattern of the 5 TTF-1/Napsin A negative non-mucinous LADCs included solid/trabecular/basaloid patterns (Figure 1). Interestingly, 2 cases showed mixed positive TTF-1/Napsin A in better differentiated acinar/papillary patterns and negative TTF-1/Napsin A in poorly differentiated (solid/nested) areas (Figure 2). Overall, of the 10 *STK11*-mutated LADCs containing poorly differentiated (solid/nested/trabecular/basaloid/complex glandular) patterns, 8 (80%) exhibited TTF-1/Napsin A negativity in poorly differentiated components. In contrast, all the LADCs with better differentiated patterns (acini/papillary/lepidic) were positive for TTF-1/Napsin A (Figure 3). All cases, regardless of growth pattern, were diffusely CK7 positive. Of the 6 mucinous LADCs, 3 had IHC, of which 1 was TTF-1/Napsin A negative, and 2 were TTF-1/Napsin A positive.

Of the 2 *STK11*-mutated mucinous LADCs with *SMARCA4* deficiency, 1 was TTF-1 positive, and 1 was TTF-1 negative. The 1 non-mucinous LADC with *SMARCA4* deficiency showed a basaloid/adenoid cystic-like pattern and was TTF-1 negative.

Clinical Outcome of Patients With *STK11*-Mutated LADCs

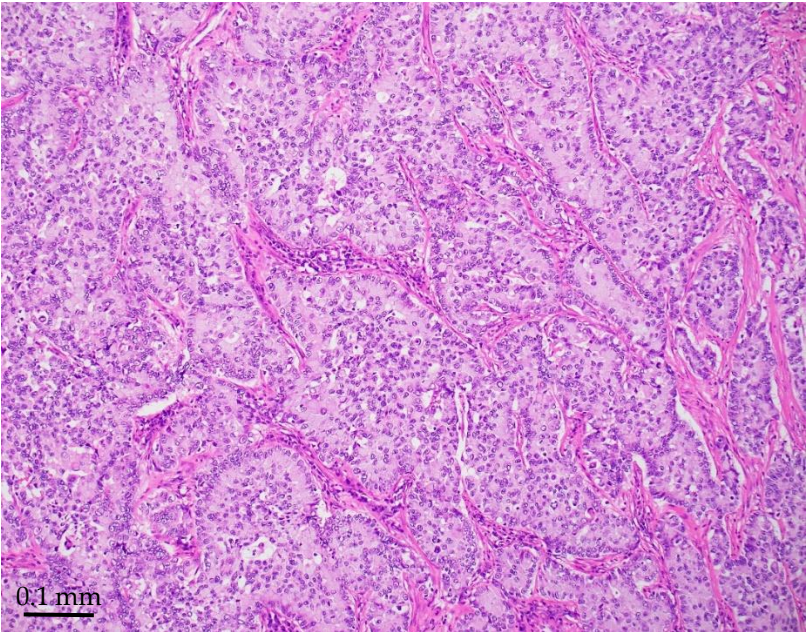
Of the *STK11*-mutated LADC patients with available follow-up, the majority (14/21, 67%) presented with metastases.

The molecular, morphologic, and IHC findings, as well as the clinical follow-up, are summarized in Table 1.

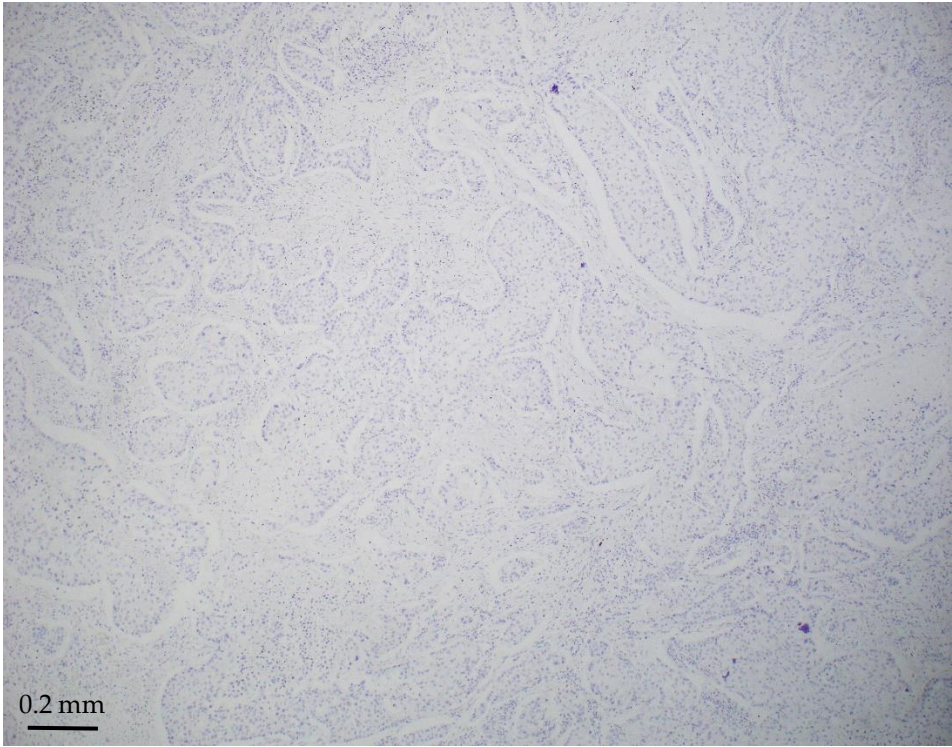


(A)

Figure 1. Cont.

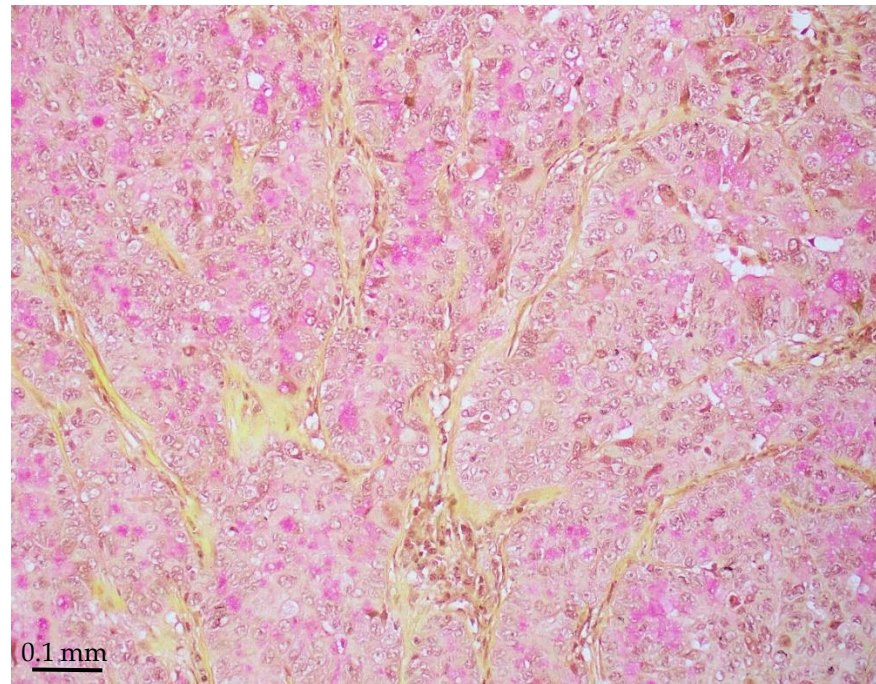


(B)



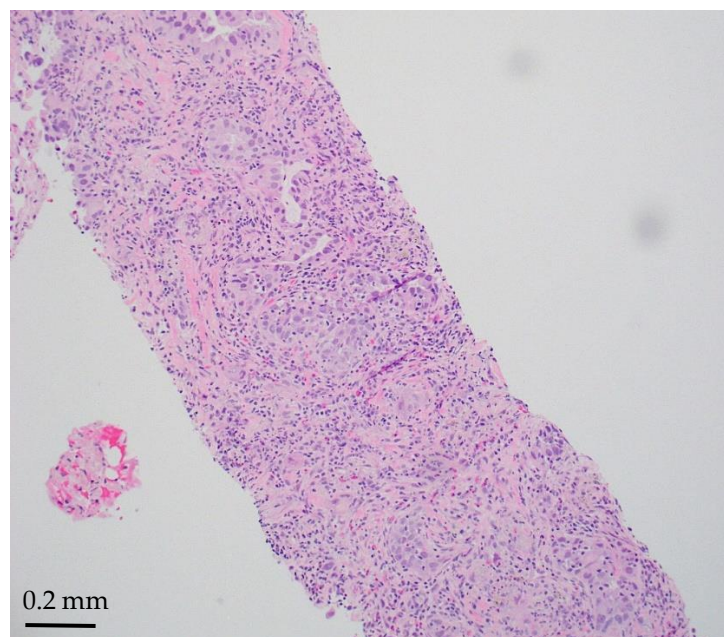
(C)

Figure 1. Cont.



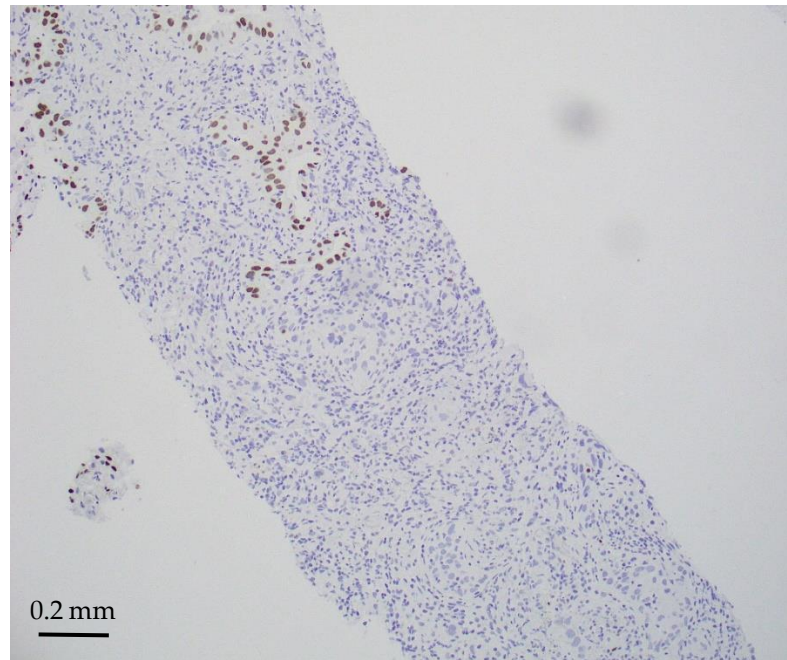
(D)

Figure 1. *STK11*-mutated LADC with poorly differentiated growth patterns. (A) Solid pattern (H&E, magnification $\times 150$). (B) Peripheral palisading basaloid pattern (H&E, magnification $\times 300$). (C) Negative for TTF-1 (magnification $\times 150$). (D) Positive for Mucicarmin (magnification $\times 300$).



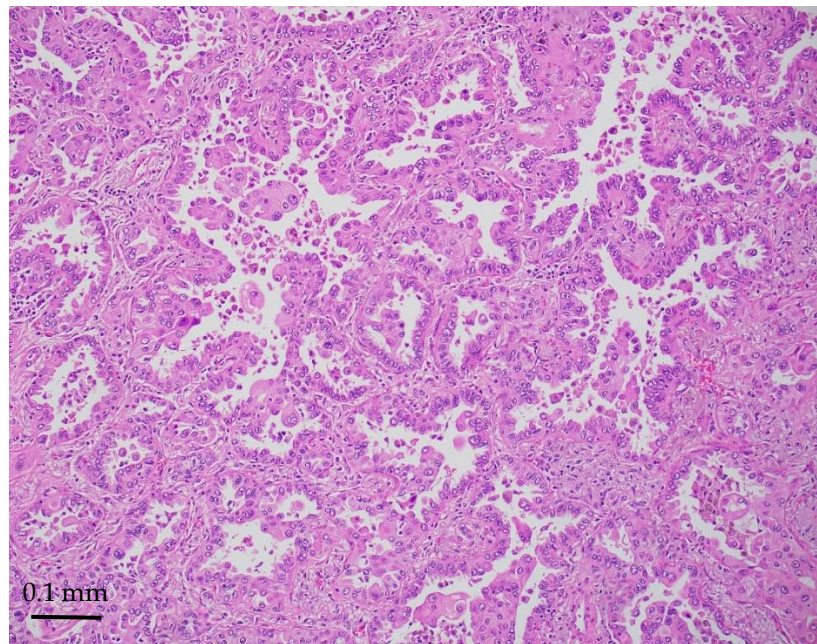
(A)

Figure 2. *Cont.*



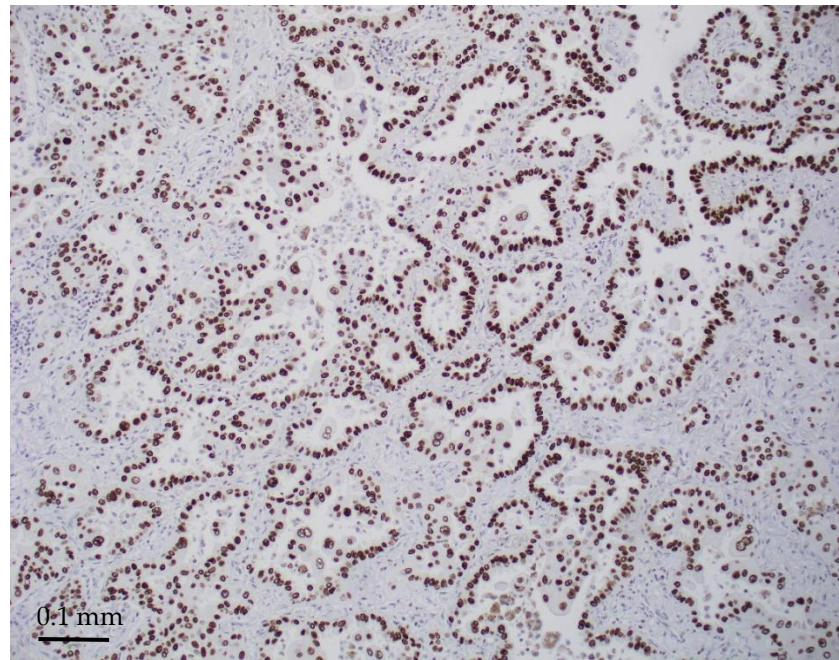
(B)

Figure 2. *STK11*-mutated LADCs with mixed solid and acinar patterns (magnification $\times 150$). (A) Mixed solid (lower) and acinar (upper) patterns (H&E); (B) TTF-1 negative in solid pattern (lower) and positive in acinar pattern (upper).



(A)

Figure 3. *Cont.*



(B)

Figure 3. *STK11*-mutated LADCs with better differentiated patterns (acinar/papillary) (magnification $\times 300$). H&E stain (A) and diffusely TTF-1 positive (B).

Table 1. Molecular and clinicopathologic features of *STK11*-mutated LADC.

Age/ Sex	Morphology	Smoking History	IHC (TTF-1/Napsin A, CK7 and p40)	Other Associated Gene Alterations in Addition to <i>STK11</i>	PD-L1/TPS (%)	TMB (mut/Mb)	MSI	Follow Up (Recurrence and Metastasis)	Stage
92/M	Mucinous	Yes	TTF-1+, CK7+	<i>BRCA2, KRAS, RNF43, SMARCA4</i>	0	11	MSS	Lost to follow-up	NA
69/M	Mucinous	Yes	TTF-1+, Napsin A+, p40-	<i>KRAS, POT1, TP53</i>	23	9	MSS	No recurrence or metastasis	T2aN0
79/M	Mucinous	Yes	NA	<i>ATM, KRAS</i>	0	8	MSS	Lost to follow-up	T1aN0
78/M	Mucinous	Yes	TTF-1-, Napsin A-	<i>EGFR, NFKBIA, KRAS, RBM10 SMARCA4</i>	0	4	MSS	Metastasis to bone, pleura and lymph nodes	NA
86/M	Mucinous	Yes	NA	<i>KRAS, NKX2.1</i>	0	4	MSS	Recurrence in lung	NA
83/F	Mucinous	Yes	NA	<i>KRAS, U2AF1</i>	0	8	MSS	Metastasis to brain	NA
80/M	Acinar, papillary	Yes	NA	<i>KEAP1</i>	0	5	MSS	No recurrence or metastasis	T2aN0
81/M	N/A	Yes	TTF-1+, Napsin A+, CK7+, P40-	<i>TP53, BCOR, MYC, NF1, NFE2L2</i>	0	17	MSS	Metastasis to lymph nodes	NA
53/M	Small solid nests	Yes	TTF-1-, Napsin A-, p40-, CK7+	<i>TP53, ARID2</i>	0	7	MSS	Metastasis to lymph nodes	NA
82/M	Acinar	Yes	TTF-1+, Napsin A+, P40-	<i>CCNE1, KRAS</i>	0	7	MSS	Metastasis to lymph nodes	NA
73/M	N/A	Yes	TTF-1+, Napsin A+, CK7+	<i>KRAS, TP53</i>	0	15	MSS	Metastasis to lymph nodes, bone and brain	NA
65/F	Cribriform, solid	Yes	TTF-1+, Napsin A+, CK7+	<i>CCNE1, MAP2K1 (MEK1), TP53</i>	0	13	MSS	Metastasis to brain	NA

Table 1. Cont.

Age/ Sex	Morphology	Smoking History	IHC (TTF-1/Napsin A, CK7 and p40)	Other Associated Gene Alterations in Addition to <i>STK11</i>	PD-L1/TPS (%)	TMB (mut/Mb)	MSI	Follow Up (Recurrence and Metastasis)	Stage
78/F	Basaloid, adenoid cyst-like	Yes	TTF-1-, Napsin A-, p40-, CK7+	<i>KRAS, STK11, SMARCA4, APC, KEAP1</i>	0	10	MSS	Metastasis to brain and bone	T1cN0
71/M	N/A	No	TTF-1+, Napsin A+	<i>ATM, KRAS</i>	3	3	MSS	Lost to follow up	NA
64/M	N/A	Yes	TTF-1+, Napsin A+, Ck7+	<i>DNMT3A, KEAP1, TP53</i>	2	12	MSS	Metastasis to liver, deceased	NA
82/F	Small nests, trabecular	No	NA	<i>MDM2</i>	0	2	MSS	Metastasis to bone	NA
82/M	Solid, acinar	Yes	Solid: TTF-1-, Napsin A-; acinar: TTF-1+, Napsin A+	<i>MGA, PRKDC, TP53</i>	1	13	MSS	Lost to follow-up	T2aN0
62/M	Trabecular, solid	Yes	TTF-1-, Napsin A-, p40-, CK7+	<i>ATM, KEAP1, KRAS</i>	100	11	MSS	Metastasis to lymph nodes	T1cN2
70/M	Acinar, complex glandular pattern	Yes	acini: TTF-1+; complex glands: TTF-1-	<i>TP53, ARID2, PDGFRA</i>	0	9	MSS	No recurrence or metastasis	T1cN0
77/F	Solid, basaloid	Yes	TTF-1-, p40-	<i>KEAP1, KRAS, RBM10</i>	1	10	MSS	Recurrence in lung	T2bN0
69/M	Acinar, solid nest	Yes	TTF-1+, Napsin A+, CK7+	<i>CTNNB1, TP53</i>	0	13	MSS	No recurrence or metastasis	yT3N2
59/M	Basaloid, solid nest	Yes	TTF-1-, Napsin A-, p40-, CK7+	<i>TP53, KEAP1</i>	7	4	MSS	Metastasis to scalp	NA
73/M	Acinar, papillary	No	TTF-1+, CK7+	<i>BRCA2, KEAP1</i>	0	4	MSS	Metastasis to pleura	NA

Table 1. Cont.

Age/ Sex	Morphology	Smoking History	IHC (TTF-1/Napsin A, CK7 and p40)	Other Associated Gene Alterations in Addition to <i>STK11</i>	PD-L1/TPS (%)	TMB (mut/Mb)	MSI	Follow Up (Recurrence and Metastasis)	Stage
70/M	Lepidic, acinar, papillary	Yes	NA	<i>ARID2, TP53</i>	15	10	MSS	No recurrence or metastasis	pT1cN0
84/F	Lepidic, acinar, papillary	No	NA	<i>KEAP1, MYC, RAF1, TET2</i>	0	5	MSS	No recurrence or metastasis	pT1bN0
72/M	Lepidic, acinar, papillary	No	NA	<i>KRAS, NFE2L2</i>	0	6	MSS	No recurrence or metastasis	pT1cN0
83/M	Acinar, papillary	Yes	TTF-1+, Napsin A+, p40-, CK7+	<i>KRAS, RUNX1</i>	0	11	MSS	Lost to follow-up	NA
62/M	Acinar, solid, nested	No	solid: TTF-1-, CK7+; acinar: TTF-1+, CK7+	<i>ATM, KEAP1, KRAS, TGFBR2</i>	90	11	MSS	Metastasis to lymph nodes	T1cN2
64/F	Lepidic, acinar, papillary	Yes	NA	<i>BRAF, FAT1, KEAP1, MET, U2AF</i>	0	8	MSS	Lost to follow-up	pT1bN0
63/M	LCNEC	Yes	TTF-1-, Napsin A-, p40-, CK7+, NE markers+	<i>RB1, TP53, EED, JAK2, KRAS</i>	3	47	MSS	Metastasis to brain	NA

M: Male; F: female; PD: Poorly differentiated; NA: Not available/not applicable due to small amount of tumor or not available or not performed; LCNEC: Large cell neuroendocrine carcinoma; NE: Neuroendocrine.

4. Discussion

This study demonstrated that the vast majority (97%) of *STK11*-mutated lung cancers were LADC. *STK11* mutation occurred in 26% of the LADCs, which, after taking into consideration the potential difference in the study population, is similar to the 17–20% reported in the TCGA (The Cancer Genome Atlas) database [16]. Like general LADC, *STK11*-mutated LADC was strongly associated with smoking history, and predominantly in male patients. *STK11* mutations were found in both mucinous and non-mucinous LADCs. The most common concurrent altered gene with the *STK11* mutation was *KRAS*, followed by *TP53*, *KEAP1*, and DNA repair genes (*BRCA 1/2* and *ATM*). Tumor suppressor and DNA repair gene alterations appeared to be mutually exclusive. The targetable gene alterations *EGFR*, *ROS*, and *ALK* were rare or not found to concur with the *STK11* mutation. Except in a rare case of LCNEC, the *STK11* mutation was not found in non-LADC tumors.

The histomorphology of *STK11*-mutated LADCs was variable. Concurrence of *STK11* with *KRAS* mutation could be either mucinous or non-mucinous phenotypes. All the *STK11*-mutated mucinous LADCs had concurrent *KRAS* alteration; however, concurrent *STK11* and *KRAS* mutation did not always present with mucinous morphology. Interestingly, LADCs with concurrent *STK11* and *KEAP1* mutations (10 of 10 cases) never exhibited mucinous morphology, even in cases with concurrent *KRAS* mutations (4 of 4 cases).

Immunohistochemically, about half of the *STK11*-mutated non-mucinous LADCs were TTF-1/Napsin A negative, much more common than the non-mucinous LADCs in general (~10%), of which all were poorly differentiated with a solid/trabecular/basaloid growth pattern.

It has been reported that *KRAS* mutation silences *NKX2.1/TTF-1* by methylation of its promoter, leading to downregulation of TTF-1 [17]. Loss of TTF-1 in *KRAS*-mutant cells is related to increased activation of the ERK signaling pathway, which promotes cancer cell proliferation and migration and is associated with mucinous LADC [18]. This event might account for the TTF-1 negativity in *KRAS*-mutated mucinous LADCs, as well as some *KRAS*-mutated non-mucinous LADCs, as seen in this study. These features are also important for practicing pathologists to recognize that, when TTF-1/Napsin A negative, non-mucinous, poorly differentiated LADCs are encountered, *STK11*-mutated LADCs should be considered. In addition, given the common association of negative TTF-1 with poorly differentiated morphology, loss of TTF-1 may be used as a predictor for aggressive behavior.

SMARCA4-deficient lung cancer can be classified as thoracic SMARCA4-deficient tumors or SMARCA4-deficient non-small cell lung cancer. Histologically, SMARCA4-deficient thoracic tumors are often poorly differentiated or undifferentiated. In contrast, SMARCA4-deficient non-small cell lung cancer exhibits a broad spectrum of morphological features [19–22]. As shown in this study, SMARCA4-deficient LADC with *STK11* co-mutation can present with mucinous or basaloid morphology.

The frequent association of *STK11* mutation with *TP53* and DNA gene repair mutations, as well as poor differentiation in morphology, is in keeping with the aggressive nature and poor prognosis of these tumors.

In addition to MSS, except for cases with concurrent *ATM* and *STK11* mutations, the low PD-L1 TPS in most *STK11*-mutated LADCs may imply poor responses to PD-L1/immune checkpoint inhibitors (ICI), which seems to be in line with the results of other studies [16,23–25].

STK11 is a tumor suppressor gene. One of its roles is acting as an inhibitor of *mTOR* signaling. When *STK11* is mutated, the *mTOR* pathway becomes hyperactivated, resulting in increased cell growth and proliferation. Additionally, *STK11* inactivation creates a pro-growth and inert tumor immune microenvironment, including reduced density of infiltrating cytotoxic CD8⁺ T lymphocytes, a low expression of PD-L1 in the tumor, an

immune-suppressive neutrophil-enriched niche, and inactivation of the STING (stimulator of interferon genes) pathway. These events can contribute to not only tumor development/progression but also immune evasion and resistance to ICI [26–28]. The combination of *STK11*, *KRAS*, and/or *KEAP1* mutations has been shown to confer worse prognosis and survival outcomes [29–33].

Given the low expression of PD-L1 and inert immune microenvironment in *STK11*-mutated LADCs (with or without *KRAS* and/or *KEAP1* co-mutation), new strategies for treatment are being explored for these patients. Combining two ICIs (e.g., anti-PD-L1 and anti-CTLA-4) with chemotherapy has shown greater effectiveness than either treatment alone in retrospective studies [27–29]. Blocking IL-6 has shown some success in preclinical models by decreasing tumor proliferation and improving T-cell function [27,28]. For patients with the specific *KRAS* p.G12C subtype, targeted inhibitors like sotorasib and adagrasib are available. *KEAP1* mutations activate the NRF2 pathway [30,31]. As the activation of the NRF2 pathway is a key driver of resistance, inhibition of NRF2, particularly in combination with PD-L1 inhibition, has shown promising results in some cancer types [27,29].

Of note, our study showed that almost half (45%) of the *STK11*-mutated LADCs had TMB ≥ 10 . These patients with high TMB may have better responses to ICI than patients with low TMB. In addition, the frequent DNA repair gene mutations (*BRCA2* and *ATM*, 21%) may qualify these patients for treatment with a PARP inhibitor. Therefore, further stratification of these patients in a personalized manner may be beneficial in achieving optimal outcomes. Future studies using recently developed tools, such as Multi-omics Immuno-Oncology Biologic Research (IOBR), to uncover the immune microenvironment in these tumors and design new immunotherapeutic regimens are warranted [34].

In conclusion, *STK11*-mutated LADCs have unique attributes. Recognition of this molecular entity will not only have prognostic and therapeutic implications but may also have diagnostic value in daily practice. Testing for *STK11* mutation may be included in the existing panel of routine molecular tests for pulmonary adenocarcinomas. More recently, STK11 IHC staining has become available, leading to more convenient biomarker assessment [26–35].

This study is limited by the relatively small sample size, lack of robust clinical follow-up data, potential case selection bias (e.g., referral for testing, sample adequacy), and the retrospective nature of the study design, as well as assay/threshold differences that could have affected prevalence, PD-L1, and TMB distributions. Large cohorts and more comprehensive studies are warranted to validate the results.

Author Contributions: Conceptualization, G.-Q.X.; Methodology, J.J. and G.-Q.X.; Validation, J.J., W.D.W. and G.-Q.X.; Formal analysis, J.J. and G.-Q.X.; Data curation, J.J. and G.-Q.X.; Writing—original draft, J.J. and G.-Q.X.; Writing—review & editing, J.J., W.D.W. and G.-Q.X.; Supervision, G.-Q.X. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the USC Institutional Review Board (HS-24-00234). The date for ethical approval is 22 September 2022, and recertified on 11 July 2025.

Informed Consent Statement: There is no need patient's consent because the use of archived/paraffin-embedded tissue and pts consent is waived.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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